## REMARKS

Upon entry of this Amendment, claims 1, 7-19, 30 and 31 are pending in the application and presented for examination. Claims 1, 7-8, 13, 15-16, 19, 30 and 31 have been amended. Claim 6 has been canceled without prejudice or disclaimer. Applicants respectfully request claims 9-14 be reinstated. Applicants believe no new matter is present in this or any other portion of the present amendment.

Reconsideration of the application is respectfully requested in view of the above amendments to the claims and the following remarks. For the Examiner's convenience and reference, Applicants' remarks are presented in the order in which the corresponding issues were raised in the Office Action.

### I. STATUS OF CLAIMS

The Examiner objected to claims 6 and 12 as being dependent on a rejected base claim, but stated that claims 6 and 12 would be allowable if rewritten in independent form including all the limitations of the base claim. As suggested by the Examiner, the features of claim 6 have been incorporated into claim 1 and claim 6 has been canceled without prejudice. Claim 12 has been amended to be dependent on the amended claim 1.

### II. CLAIM OBJECTIONS

The Examiner objects to claim 31 as allegedly being of improper dependent form. Applicants have amended claim 31 to be dependent on claim 1. Accordingly, Applicants request that the Examiner withdraw the objection.

### III. REJECTION BASED ON 35 U.S.C § 112, FIRST PARAGRAPH

Claims 1, 7-8, 15-19 and 30-31 were rejected under 35 U.S.C. § 112, first paragraph as allegedly the specification enables only a method for the production of HCAM resin and does not reasonably provide enablement for all methods for production

of all derivatized resins encompassed by the definition of formula (I). In response, Applicants respectfully traverse the rejection.

Applicants assert that the claims of the present invention find sufficient enabling support throughout the specification. Any analysis of whether a claim is enabled by the disclosure in an application requires a determination of whether the disclosure contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. Applicants present such analysis of claims 1, 6-19-3- and 31 in view of the factors set forth *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). These factors include, for example, **(1)** breadth of claims, **(2)** nature of the invention, **(3)** state of the prior art, **(4)** level of one of ordinary skill, **(5)** level of predictability in the art, **(6)** amount of direction provided by the inventor, **(7)** existence of working examples, and **(8)** quantity of experimentation needed to make or use the invention.

The Examiner alleges that while the breadth of claim **(1)** of the present invention encompass methods for production of a derivatized resin, including amide-, imine- and thioamide-based resins, the examples in the specification teach the production and use of only amide based resins. Applicants respectfully disagree and maintain that enabling support for all claims, including the claims encompassing thioamide- and imine-based resin, are found in the specification.

Applicants respectfully direct the Examiner's attention to the section entitled "b. Reactants and Synthetic Routes for Production of the Derivatized Resin of Formula (I)" on page 14 of the present application. In this section, four synthetic routes for the preparation of all the derivatized resins claimed in the present invention are set forth (*see*, pages 16-19, "Synthetic Routes 1-4"). One skilled in the art would recognize in Synthetic Route 1, for example, that if X is S for reagent (B) R1-(C=X)-R2 then the product (I) of this route would be a thioamide-based resin. In addition, one skilled in the art would recognized other straightforward variation of reagents in synthetic routes 2-4 that would also produce thioamide- and imine-based resins (*see*, page 21 line 29 to page 30 line 1).

In particular, exact reagents used for synthesizing thioamide- and imine-based resins are taught in Synthetic Route 3 (*see*, page 17 line 9, to page 18 line 2). Route 3, specifies that reagent (AA) (*see*, page 17 line 15) be a suitable thioisocyanate when X is sulfur, and is a suitable carbodiimide (AA) when X = N-R7.

An even more detailed description of the methods for making thioamide- and imine-based resins is found in the section title "c. Embodiments and Variations on Synthetic Routes 1-4 for Production of the Derivatized Resin (I) of Formula R4-NH-(C=X)-Y-Z-SS", on page 19 of the instant application. For example, a method to make thioamide-based resin when Y is absent, or -CH2- and X is S is taught on page 20, lines14-26, where the amide product (IB) R4-NH-(C=O)-Y-Z-SS is treated with a thionating reagent to form the thioamide-based resin product (R4-NH-(C=S)-Y-Z-SS). A method to make an imine-based resin when Y is absent or -CH2- and X is NR7 is also taught on page 21, lines 4-22, where the thioamide product (IB) R4-NH-(C=S)-Y-A-SS is alkylated to form product (H) R4-N=(C-S-R11)-Y-Z-SS, which is further reacted with N-R7 to form the imine-based resin product (ID) R-NH-(C=NR7)-Y-Z-SS.

The examples of the specification use amide-based resins (HCAM) to illustrate the synthetic methods described above. However, one skilled in the art would readily recognized other reagents encompassed within the described methods of Synthetic Routes 1-4 that would provide for thioamide- and imine-based resin products. For example, in Example 1 (*see*, page 42 line 6), one skilled in the art would recognize that substituting the reagent of example 1,1,1-carbonyldiimidazole, with 1,1-thiocarbonyldiimidazole would produce the thioamide product. Accordingly, the breadth of the claims teach the production of amide-, thioamide-, and imine-based resins of the present invention.

The nature of the invention (**2**) is for the synthesis of derivatized resins, specifically for amide-, thioamide-, and imine-based resins. In this regard, Applicants respectfully disagree with the Examiner's allegation that the exact components used in the method steps cannot be determined for thioamide- and imine-based resins in the specification. The exact components used for thioamide- and imine-based resins are

disclosed in the specification. Applicants respectfully point out to the Examiner that Synthetic Route 3 (*see*, page 17, starting on line 11) teaches a thiocyanate (*see*, page 17 line 23) reagent as the reagent used to make a thioamide-based resin, and a carbodiimide (*see*, page 17 line 24) reagent as the reagent used to make an imine-based resin. One skilled in the art would recognize other variation of reagents that would produce thioamide- and imine-based resins.

The Examiner cites factors (**3**) and (**5**) of *In re Wands*, alleging that the state of the art and the level of predictability in the art cannot be predicted as to how specific resins other than amide-based resins can be produced or used in the solid phase synthesis. In response, Applicants respectfully traverse the allegation.

Applicants emphasize that to tailor the synthetic method disclosed in Synthetic Routes 1 and 2 to prepare a thioamide- or imine-based resin instead of an amide-based resin, only one reagent of the method (reagent (B)) is changed (*see*, page 16, line7 to page 17, line 7). To prepare a thioamide based resin, reactant (B) would have the formula R1-(C=S)-R2, such as 1,1-thiocarbonyldiimidazole (*see*, page 16, line 15). To prepare an imine-based resin, reagent (B) would have the formula R1-(C=N)-R2, as in imine diimidazole. Within the art, the (C=X) functional group of the R1-(C=X)-R2 is recognized as a electrophilic site and the reagent R1-(C=X)-R2 is used to introduce a (C=X) group onto a molecule (*see*, page 16 lines 13-20). The reactivity of the reagent R1-(C=X)-R2 is reliable, and does not vary whether X is S or N or O.

Furthermore, amide-, thioamide-, and imine-based resins are prepared from the reaction of (-Y-Z-SS) with a ketene-imine equivalent [R4-NH=(C=X)-R2], such as an isocyanate (R4-N=C=O), a thiocyanate (R4-N=C=S), or a carbodiimide (R4-N=C=NR) (*see*, Synthetic Route 3, page 17 line 9 to page 18 line 2). Within the art, it is recognized that ketene-imine equivalents are electron deficient reagents and have similar chemical reactivity. The ketene-imine carbon (R4-N=**C**=X) is an electron deficient *sp*-hybridzed carbon and is susceptible to nucleophilic attack. Furthermore, Applicants point out that as described in Synthetic Route 3 of the specification, variation of the ketene-imine

species used does not require any change to the established synthetic route. As such, the synthetic route described for the thioamide- and imine-based resins are predicable based on the working examples provided for the related amide-based resins. Using the working examples of the specification, one skilled in the art could simply substitute, for example, a reagent where X=O with one where X=S or NR7, to produce the corresponding thioamide- or imine-based resin. Contrary to the allegation of the Examiner, the state of the art and the level of predictability of the chemical reactivity of the reagents R1-(C=X)-R2 and R4-NH=(C=X)-R2 are well established.

Citing factors **(4)** and **(6)** of *In re Wands*, the Examiner alleges that the inventor provides no guidance beyond the methods taught for amide-based resins. As a result, one of ordinary skill could not predict what components and alternate synthesis steps are necessary in the synthesis or production of resins other than amide based resins. Applicants respectfully disagree with the Examiner's conclusion.

The specification teaches not only a method of preparing amide-based resin, but also teaches a method for preparing thioamide-, and imine- based resins. One of ordinary skill does not have to predict what components and alternate synthesis steps are necessary in the production of resins other than amide-based resins as these components and reagents are already disclosed in the specification. In this regard, Applicants direct the Examiner's attention to the method disclosed in Synthetic Route 3 (*see*, page 17, line 9 to page 18 line 2, "Route 3"). In Route 3, a thiocyanate reagent (AA) is the reagent specified in the synthetic route when preparing a thioamide-based resin, and a carbodiimide reagent (AA) is the reagent specified for a synthesis of an imine-based resin. According to the method, the synthetic route is not altered when the reagent (AA) is changed.

Applicants maintain that the specific examples taught in the specification are sufficient to guide one skilled in the art to prepare thioamide- and imine-based resins. For example, one skilled in the art would recognized that the reagent used in the synthesis of the amide-based resin described in Example 1 (*see*, page 42, line 6), 1,1-

carbonyldiimidazole, could be replaced by the reagent, 1,1-thiocarbonyldiimidazole, when the synthesis of the thioamide-based resin was desired. Other reagent substitutions would be readily apparent to one skilled in the art.

Citing *In re Wands* factors (**7**) and (**8**), the Examiner alleges the existence of working examples are limited to teaching the synthesis of a specific amide-based resin (HCAM) and that an indeterminant quantity of experimentation would be necessary to determine all potential or alternate type of methods for the synthesis of derivatized resins, other than amide based resins, such as thioamide- and imine-based resins. In response, Applicants traverse the allegation.

The working examples in the specification illustrate a method for the synthesis of an amide-based resin. Applicants maintain that it would not require an indeterminant quantity of experimentation of determine the method for the synthesis of other derivatized resins such as thioamide-, and imine-based resin. One skilled in the art would be able to see that substituting a reagent of Example 1 (*see*, page 42 line 6), 1,1-carbonyldiimidazole, with, for example, commercially available 1,1-thiocarbonyldiimidazole would result a thioamide-based resin product. Further, one skilled in the art would recognize additional straightforward modification of the reagent in Example 1 that would produce thioamide-and imine-based resins. The reactivity of the 1,1-thiocarbonylimidazole and the 1,1-carbonyldiimidazole are similar and as such would not require any change to the synthetic route. Accordingly, no further experimentation would be needed in the synthesis of the thioamide- and imime-based resins.

In summary, Applicants have shown that claims 1, 7-8, 15-19, 30 and 31 of the present invention find enabling support throughout the specification. As such, Applicants respectfully request that the rejection of claims 1, 7-8, 15-19, 30 and 31 be withdrawn. Furthermore, Applicants request that claims 9-14, claims dependent on claim 6, that address methods for synthesizing thioamide- and imine-based resins be reinstated and considered allowable in the present application.

**IV. REJECTION BASED ON 35 U.S.C § 112, SECOND PARAGRAPH**

The Examiner has rejected claims 1, 7-8, 15-19, 30 and 31 as indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respond in-part by amendment and in-part traverse the rejection.

a. The Examiner alleges that the term "derivatized resin" is unclear as the specification, claims and art do not recognized what "derivatized" means. In response, Applicant's respectfully traverse the rejection.

The term "derivatized" has a clear definition. As defined in Merriam-Webster dictionary, "derivatize" is the conversion of a chemical compound into a structurally related substance. As used in the present invention, the term "derivatived resin" has the meaning of a resin that has been converted to another structurally related resin. Examples of how a resin is converted to a derivatized resin, or more specifically, what chemical functional group manipulations or transformations result in a "derivatized" resin are found throughout the specification (*see*, pages 16-19, Synthetic Routes Nos. 1-4). For example, in Synthetic Route 1, a resin (A) R-Y-Z-SS is reacted with a reagent of formula (B) R1-(C=X)-R2 to form an intermediate product of formula (C) R1-(C=X)-Y-Z-SS. Intermediate (C) is then reacted with a reagent of formula (D) R4-$NH_2$ to form the *derivatized resin* product (I) of formula R4-NH-(C=X)-Y-Z-SS. The steps outlining the conversion of a resin to a derivatized resin is clear and distinct. Accordingly, Applicants respectfully request that the rejection be withdrawn.

b. The Examiner alleges that the term "a protecting group" used in reference to R4 of claim 1 is unclear as the art does not recognize what the generic "protecting group" defines. In response, Applicants respectfully traverse this rejection.

The term "protecting group" is clearly defined in the specification (*see*, page 8, lines 6-17). A "protecting group" is a moiety that has the desirable property of preventing specific chemical reactions at a site on a molecule undergoing chemical

modification intended to be left unaffected by the particular chemical modification, while at the same time being easily removed from the molecule. Examples of protecting groups described within the specification include Cbz, Boc, Alloc, Fmoc, Troc, Teoc, $(Me_3Si(CH_2)_2OCO)$, and PMC. Those skilled in the art would recognized other protecting groups suitable for use in the invention. As the term "protecting group" is clearly defined within the specification, Applicants respectfully request that the rejection be withdrawn.

Furthermore, in claim 1, the Examiner rejects to the use of the terms "and combinations thereof" and "under conditions for peptide synthesis" alleging that the metes and bounds of these terms cannot be determined as the specification, claims, and art do not recognized what the generic terms define. In response, Applicants have amended the claims to omit these alleged indefinite terms. As such, Applicants believe the concerns of the Examiner have been obviated. Accordingly, Applicants request that the rejection be withdrawn.

c. The Examiner alleges there is insufficient antecedent basis for the use of the following limitations in claim 1: [1] in the preamble "the formula (I), [2] in step (i) "the product (I)", and [3] in step (ii) "the derivatized resin" (I). In response, Applicants have amended claim 1 as follows: the preamble now recites "formula (I)"; step (i) now recites "derivatized resin" (I); step (ii) now recites "derivatized resin" (I). In view of these foregoing amendments, Applicants respectfully request that the rejection be withdrawn.

d. The Examiner alleges claim 6 is vague and indefinite for the recitation of the terms "R1 is a leaving group" and "R2 is a leaving group, same or different than R1". Claim 6 has been cancelled without prejudice. However, as this language is present in claim 1, Applicants proceed to address the rejection.

The Examiner alleges that the art does not recognize what the generic term "leaving group" is and as such how a "leaving group" can be the "same or different than"

relative to another leaving group without knowing the identity of such groups. Applicants respectfully traverse this rejection.

Applicants point out that the use of the term "leaving group" finds basis within the specification (*see*, page 7 line 26-27 to page 8 lines 1-4). Specific examples of "leaving groups" are found on page 8, lines 2-4, of the specification and include, but are not limited to, hydrogen, hydroxyl radicals, halogen atoms, p-nitrophenoxide, and water. As the term "leaving group" is clearly defined along with specific examples given in the present application, there is no ambiguity to the term "leaving group" and the reference to a "leaving group same or different than R1 (R1 = another leaving group)". Accordingly, Applicants request the rejection be withdrawn.

e. The Examiner alleges that claim 15 is vague and indefinite for reciting the following term: "R4 is converted to a reactive derivatized resin bearing a free amine by removal of R3." The Examiner alleges the art does not recognize what the generic term "reactive" defines. In response, Applicants have amended the claim to omit the term "reactive." As such, Applicants respectfully request that the rejection be withdrawn.

f. The Examiner again rejected the use of the term "reactive derivatized resin" in claim 16. Applicants respond in-part by amendment, and in-part by traverse. Applicants amended the claim to omit the term "reactive," but maintain that use of the term "derivatized resin" as explained above.

Furthermore, the Examiner alleges the term "appropriately protected aldehyde or ketoamide" is indefinite. Applicants respond in-part by amendment, and in-part by traversing the rejection.

Applicants amended claim 16 to omit the term "appropriately". Basis for the use of the term "protected aldehyde or ketomide" is found in the specification on pags 27 line 6, through page 30 line 16. All the characteristics of a "protected" peptide, peptide analog, and peptidomimetic compounds along with specific examples of suitable protecting groups are described. In addition, on page 32, line 30, to page 33, line 1-17 of the specification, is described a preferred example of a "protected aldehyde" for the case

wherein the aldehyde is argininal. The "protected aldehyde" is one that is orthogonally protected where the side-chain amino group is di-alloc or di-boc protected and the argininal amino terminal nitrogen is Fmoc protected (*see*, page 33, lines 7-10). One skilled in the art would be aware of other protecting groups that would be suitable for an aldehyde or ketoamide of the instant invention. In light of the detailed example provided in the specification describing what a "protected aldehyde and ketoamide" is, Applicants believe the term is clear and definite in the present invention and request that the rejection be withdrawn.

g. The Examiner alleges claim 18 is vague and indefinite due to the recitation of the following phrase "wherein said aldehyde is orthogonally protected." Applicants respectfully traverse the rejection.

For clarification, the term "aldehyde" used herein, refers to a peptide aldehyde. Orthogonal protection refers to protection of the α-amino group and the side-chain amino group of the peptide aldehyde. The specification on page 33, lines 6-12 clearly describes what constitutes an orthogonally protected aldehyde. For example, line 6, on page 33 sets forth:

> "in one preferred example of orthogonal protection, it is preferred for the argininal side-chain amino group to be di-alloc or di-boc protected, and the argininal amino terminal nitrogen be Fmoc protected."

The implication of the choice of protecting group is further stated in the next sentence which reads:

> "In this manner, Fmoc peptide synthesis may be safely conducted, without the danger of deprotection of the argininal side-chain amino group in the course of subsequent peptide synthesis steps at the argininal amino terminus."

The basis for the use of the term "orthogonally protected" is clearly found within the specification, along with an illustrative example of what constitutes an orthogonal protecting group. One skilled in the art would understand other orthogonal protecting

group combinations which can be used. Accordingly, Applicants request that the Examiner's rejection be withdrawn.

h. The Examiner alleges that there is insufficient antecedent for the recitation of the term "said argininal guanidino side chain" in claim 19. In response, Applicants have amended claim 19 to recite "the argininal guanidino side chain of said aldehyde". Accordingly, Applicants request the rejection be withdrawn.

**V. 35 U.S.C § 102(b) IN VIEW OF GALPIN *ET AL.***

As suggested by the Examiner, Claim 1 has been amended to incorporate all the features of allowable claim 6. Accordingly, Applicants believe this rejection has been rendered moot.

**VI. 35 U.S.C § 102 (b) IN VIEW OF MURPHY *ET AL.***

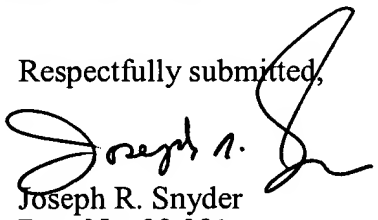
As suggested by the Examiner, Claim 1 has been amended to incorporate all the features of allowable claim 6. As such, this rejection has been rendered moot.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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